Pharmacy Friday Pearls

Phenytoin vs Keppra in Status Epilepticus

1. Status epilepticus is a neurological emeregnecy that required urgent assessment and treatment with pharmacologic agents
2. Lorazepam and diazepam are short-acting drugs that can produce immediate effects.
3. Treatment with another long-acting anticonvulsant drug is necessary to prevent recurrent convulsions.
4. Use of IV phenytoin (PHT) in the treatment of status epilepticus dates back to the 50s with fosphenytoin (FPHT) being the primary agent in some institutions.
5. However, both PHT and FPHT can induce adverse reactions such as a reduction in blood pressure, arrhythmia, and allergic symptoms.

Properties	Phenytoin/ Fosphenytoin	Levetiracetam (Keppra)
Dose	20 mg/kg/PE (max 1500 mg)	1-4.5 g IV (40-60 mg/kg)
Administration	**Max IV fusion** PHT 50 mg/min FPHT 150 mg/min	**IV Push ~3-15 min** 1.5-2g IV over 7 min** (2-5 mg/kg/min)
Formulation	IV/PO	IV/PO
PK/PD	Onset: ~30 min*** Half Life: 12-28 hr Excreted: >90% in urine	Onset: 30-45 min Half-life: 6-8 **hr** Excreted: 66% renal
Adverse Effect	Phlebitis, hypotension, bradycardia & dysrhythmias	Abnormal behavior Dizziness Irritability
Drug Interactions and warnings	Major CYP3A4 Inducer (↓ drug levels)	-----
Compatibility	PHT – only D5W FPHT- D5W or NS	D5W or NS

**PE= Phenytoin equivalents

** Fosphenytoin takes 15 mins to be metabolized to active metabolite in addition to the infusion time

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Is Levetiracetam more effective in seizure control than phenytoin?

Author, Year	Design/ sample size	Dosing regimen	Outcome
EcLiPSE, 2020	RCT N= 233 pediatric patients	LEV **40 mg/kg** **vs** PHT 20 mg/kg	• There was **no difference in** cessation of convulsive status epilepticus o 70% in LEV group o 64% in the PHT group • Median time to cessation o 35 mins in LEV group o 45 in the PHT group
ConSEPT, 2019	RCT N= 286 pediatric patients	LEV **40 mg/kg** **vs** PHT 20 mg/kg	• There was **no difference in** cessation of status epilepticus at 5 mins after drug o 50% in LEV group o 60% in the PHT group
ESETT, 2019	RCT N= 384	VPA 30 mg/kg (max 3000 mg) vs LEV 60 mg/kg (max 4500mg) vs FPHT 20 mg/kg (max 1500 mg)	• There was **no difference in** cessation of status epilepticus and improvement in the level of consciousness at 60 minutes • 47% in LEV group • 45% in the fosphenytoin group • 46% in valproate group
Nakamura, 2017	*Respective analysis/ n=63	LEV 1000 mg vs FPHT 22.5 mg/kg	**No difference** in control of seizure(81 vs 85.1%, p=0.69), adverse effects, or transition to PO antiepileptic drug
Gujjar et al, 2017	*Prospective, open-label trial/ n=52	LEV 30 mg/kg vs PHT 20 mg/kg	LEV displayed **no statistically significant difference** than PHT in SE Sequential use of these 92–97% of cases controlled without anesthetic agents.
Chakravarthi, 2017	*RCT n=44	LEV **20 mg/kg** vs PHT 20 mg/kg	Both LEV and PHT were **equally effective** at termination of seizure activity within 30min and recurrence of seizures within 24 hours
Mundlamuri, 2015	RCT/ n=150	VPA **30 mg/kg** **vs** LEV **25 mg/kg** **vs** PHT 20 mg/kg	**No statistically significant difference** in control of SE between VPA (68%), PHT (68 %,) and LEV (78%).
Alvarez et al, 2011	Retrospective analysis/ n=466	VPA **20 mg/kg** LEV **20 mg/kg** PHT 20 mg/kg	VPA controlled SE in 74.6%, PHT in 58.6%, and LEV in 51.7% of episodes LEV **failed more often than VPA** [odds ratio (OR) 2.69
Answer to question: We don't know! The few studies that are published do not show a difference, however, this trial have SIGNIFICANT methological flaws that will be bias on finding no difference if one is there. The agent that is best for your patient is based on patient specific factors and drug interactions.			

* Did not reach power according to sample size analysis or did not mention in methods

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